Cerebrospinal Fluid in Posterior Reversible Encephalopathy Syndrome

Pierre R. Bourque, MD^{1,2} and Ari Breiner, MD^{1,2}

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We read with interest the article of Dr Ellis and collaborators on cerebrospinal fluid total protein (CSF-TP) levels in posterior reversible encephalopathy syndrome (PRES).¹ Isolated CSF protein elevation without pleocytosis may indeed be a valid marker of a permeability defect at the level of the blood–brain (or blood–nerve) barrier in a wide range of immune or infectious disorders of the central and peripheral nervous systems (PNS). In 77 patients with PRES, the authors noted that 60% had a CSF total protein value that exceeded the traditional “upper limit of normal” of 45 mg% (0.45 g/L), with a median value of 0.53 g/L. This modest apparent “elevation” is comparable to what was noted in other reports (eg, 0.58 g/L in the Datar et al study²).

The interpretation of CSF protein levels is however entirely dependent on the reference range chosen. Because of the challenge posed by defining institution-specific reference ranges for an invasive test, the overwhelming majority of clinical laboratories rely on published reference data. Since the seminal 1938 report of H. Houston Merritt, much of the general medical and research literature has quoted a “normal” range of 15 to 45 mg% (0.15–0.45 g/L). Worldwide hospital surveys,³ as well as national surveys from Canada and the United Kingdom, documented the persistent widespread adherence to this antiquated 0.45 g/L upper limit. We recently performed a systematic review of the laboratory reference literature for CSF total protein upper limits.⁴ This review corroborated the findings from recent large-scale normative studies in Canada and Austria which found that upper reference limits should be significantly higher and adjusted by decade of age. Using modern laboratory techniques, upper reference limits were in the range of 0.57 g/L at age 40, 0.60 g/L at age 50, and 0.63 g/L at age 60.⁵

Given that the median age was 54 years in the 77 patients who had CSF analysis, a median value of 0.53 g/L in patients with PRES suggests that the majority of patients were in fact within the reference limits supported by recent literature. The graph presented in Figure 2 reveals that a definite marked CSF-TP elevation (over 1 g/L) did occur, but only in a small subpopulation of patients with PRES. In addition, although the authors provide the total range of CSF-TP values in table 3, they do not provide the interquartile range, thus we cannot determine how the individual values cluster around the median.

The application of updated CSF-TP reference ranges would lead to a sensitivity for the diagnosis of PRES which is markedly lower than the 60% documented by Ellis et al. This would greatly reduce the usefulness of CSF-TP as a diagnostic criterion or surrogate measure of a blood–brain permeability defect in PRES. Our comment however does not intend to negate the potential interest of CSF analysis in trying to determine whether a blood–brain permeability disorder underlies the pathophysiology of PRES. Targeted studies such as the CSF/serum albumin ratio may help to address this question more conclusively.

ORCID iD

Pierre R. Bourque, MD <https://orcid.org/0000-0002-7455-0254>

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¹ Department of Medicine (Neurology), University of Ottawa, Ontario, Canada

² The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

Corresponding Author:

Pierre R. Bourque, University of Ottawa, 1053 Carling, Ottawa, Ontario, Canada K1Y4E9.

Email: pbourque@toh.ca